

REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Nuclear hormone receptors comprise a family of ligand-dependent transcription factors that have a broad effect on gene expression, growth, and development. These include the thyroid hormone receptors ("TRs") for thyroid hormone ("T3"), the retinoic acid receptors ("RARs") for all trans RA, the RARs and the retinoid X receptors ("RXRs") for 9-cis RA, vitamin D receptor ("VDR") for 1, 25-(OH)₂ vitamin D3, glucocorticoid receptor ("GR"), progesterone receptor ("PR"), estrogen receptors ("ERs"), and peroxisome-proliferation activated receptors ("PPARs"), which are regulated by variety of lipophilic compounds. These receptors share a similar modular structure consisting of an N-terminal "A/B" domain, a DNA-binding "C" domain, and a "D, E, and F" ligand binding domain ("LBD"). The LBDs of nuclear receptors are organized into twelve helical regions and the binding of ligand to the LBD of DNA bound receptor mediates a conformational change which recruits co-activators or co-regulators leading to transcriptional activation.

Co-activators which have been identified include members of the p160 family (SRC-1/NCoA-1); TIF-2/GRIP-1/NCoA-2; AIB1/p/CIP/ACTR/RAC3/ TRAM-1; the CBP/p300 family; RIP140; NRC/ASC-2/PRIP/RAP250/TRBP; PGC-1; ARA70; and NRIF3, which exhibits specificity for only the TRs and the RXRs. In addition to mediating effects of nuclear hormone receptors, certain co-activators also appear to enhance the activity of other transcription factors such as NF-kB, cFos, and cJun.

The DRIPs/TRAPs (vitamin D receptor interacting proteins/thyroid receptor-associated proteins) are another class of factors which are recruited to ligand-bound nuclear hormone receptors (e.g., VDR and TR). The DRIPs and TRAPs are multi-protein complexes which appear to be similar, if not identical, and are devoid of the p160 type of co-activators. Some of the polypeptides of the DRIP/TRAP complex also appear to be a part of the SMCC, CRSP (co-factor required for promoter specificity protein ("Sp1")) and ARC complexes. The DRIP/TRAP complexes associate with ligand-bound TR or VDR *via* a ~220-kDa component referred to as PBP/TRAP220/DRIP205 and other components of the complex interact with other transcription factors.

The association of co-activators with receptors occurs through receptor-interacting LxxLL modules of the co-activator, which bind to a hydrophobic cleft in the ligand-bound receptor formed by several regions of the LBD. The p160 family of co-

activators, RIP140, and TRAP220/DRIP205 contain multiple LxxLL motifs which is consistent with the idea that a single molecule of the co-activator can bind a nuclear receptor dimer *in vivo*.

The cloning and characterization of NRC (Nuclear Receptor Co-activator) (also referred to as ASC-2/PRIP/RAP250/TRBP) from rat and human cells which acts as a potent co-activator for nuclear hormone receptors and other transcription factors such as cFos, cJun, and NF- κ B was previously reported. NRC is organized into several modular domains which appear to play an important role in its function as a co-activator/co-regulator for nuclear hormone receptors. NRC contains one functional LxxLL motif (LxxLL-1) that binds all nuclear receptors with high affinity. This appears to occur through the formation of NRC dimers, thereby contributing two LxxLL motifs to bind nuclear receptor dimers. A region containing a second LxxLL motif (LxxLL-2) appears to be highly selective for estrogen-bound ER. NRC harbors a potent N-terminal activation domain ("AD1"), which is as active as VP16 activation domain, and a second activation domain ("AD2") which overlaps with the receptor interacting LxxLL-1 region. Receptor binding mediates a conformational change in NRC, resulting in enhanced activity of the co-activator. The C-terminal region of NRC appears to function as a modulatory domain which influences the overall activity of NRC. NRC binds CBP/p300 with high affinity *in vivo* and *in vitro*, suggesting that NRC may be an important functional component of CBP/p300 complexes in the cell.

CBP and p300, which exhibit intrinsic histone acetyl transferase activity ("HAT"), function as transcriptional integrators for multiple factors including p/CAF (a HAT), NF- κ B, the STATs, nuclear hormone receptors, the p160 family, E1A, p53, and NRC. Although NRC appears to associate with CBP *in vivo*, the identity of other factors that are part of this or other NRC complexes that play a role in the action of NRC are unknown. NRC Interacting Factor-1 ("NIF-1"), which associates with and enhances the activity of NRC *in vivo*, is a novel nuclear protein of the recently proposed BED-finger domain family containing six zinc-fingers which directly interacts with NRC but not with nuclear hormone receptors. Although NIF-1 does not bind directly to nuclear hormone receptors, it markedly enhances their ligand-dependent transcriptional activity *in vivo*. In addition, like NRC, NIF-1 also enhances the activities of cFos and cJun *in vivo*. Because nuclear hormone receptors are involved in human gene expression, and growth and development, the ability to regulate hormone receptors at the cellular level would provide a powerful tool for diagnosis and

treatment in a wide variety of human disease conditions. What is needed now is the isolation and characterization of the nucleotide sequence of a factor which regulates nuclear hormone receptors at the molecular level. Also needed are methods using such a factor for the modulation of transcription factors in human cells, so that endocrine function and cell growth and development can be manipulated for the prevention and treatment of human disease.

The present invention is directed to overcoming these and other deficiencies in the art.

The objection to claim 2 is respectfully traversed in view of the above amendments.

The rejection of claims 2 and 3 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1-7 under 35 U.S.C. 112, (1st para.) for failure to satisfy the written description requirement is respectfully traversed in view of the above amendments.

The rejection of claims 1-7 under 35 U.S.C. § 102(b) as being anticipated by Li et al., "NRIF3 is a Novel Coactivator Mediating Functional Specificity of Nuclear Hormone Receptors," Mol. Cell Biol. 19:7191-7202 (1999) ("Li") is respectfully traversed.

Li teaches the cloning and analysis of a novel nuclear receptor co-activator (designated NRIF3) that exhibits a distinct receptor specificity. Li indicates that the NRIF3 specifically interacts with the thyroid hormone receptor (TR) and retinoid X receptor (RXR) in a ligand-dependent fashion but does not bind to the retinoic acid receptor, vitamin D receptor, progesterone receptor, glucocorticoid receptor, or estrogen receptor. Li also reports that NRIF3 has no homology with any known coactivators except in a single LXXLL motif. The fact that NRIF3 contains an LXXLL motif and exhibits a distinct receptor specificity raise the possibility that either the motif and the surrounding amino acids or another region of NRIF3, are involved in mediating the receptor-specific interaction of NRIF3. However, the NIF-1 encoding nucleic acid molecule of the present application is very different from the nucleic acid molecule encoding Li's NRIF3. Accordingly, with the amendments to claim 1, the rejection based on Li is improper and should be withdrawn.

The rejection of claims 1-7 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 6,783,969 to Tang et al. ("Tang") is respectfully traversed.

Tang discloses novel nucleic acids and novel polypeptide sequences encoded by these nucleic acids and their uses. The pending claims of the present application call for

the subject nucleic acid molecule to encode a protein or polypeptide that modulates transcriptional activation in a cell with or without collaboration with a nuclear hormone receptor transcriptional co-activator. As noted in the outstanding office action, there are differences between the claimed nucleotide sequence of SEQ ID NO: 1 and that of Tung's SEQ ID NO: 68. In view of these differences, it is not proper to assume that both sequences carry out the above-noted function of Claim 1. Accordingly, the rejection based on Tang is improper and should be withdrawn.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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